Dextromethorphan Hydrobromide and Quinidine Sulfate (Nuedexta)
National Drug Monograph
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VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary:

- Current therapy for pseudobulbar affect (PBA) typically utilizes non-pharmacologic coping strategies such as relaxation and distraction techniques.
- The off-label use of selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) and dopaminergic agents has found limited success in treating PBA exacerbations.
- Dextromethorphan/quinidine (Nuedexta) is a combination of two existing generic formulary options; however quinidine is not available in an appropriate strength or in a liquid formulation (200mg, 300mg capsules only). Low dose quinidine inhibits the rapid metabolism of dextromethorphan, therefore increasing the bioavailability of dextromethorphan, resulting in effective plasma levels.
- In a double-blind, placebo-controlled study, the combination of dextromethorphan (20 or 30 mg) and low dose quinidine (10 mg) [STAR trial] significantly reduced the frequency of pseudobulbar affect episodes vs. placebo over the course of 12 weeks of treatment ($p < 0.0001$).
- Patients in the dextromethorphan/quinidine 20 mg/10 mg group reported a mean weekly episode reduction of 82% from baseline vs. a reduction of 47% in the placebo group ($p = 0.001$).
- Mean Center for Neurological Study-Lability Scale (CNS-LS) scores decreased by 8.2 points for both dextromethorphan/quinidine dosage groups vs. 5.7 points for placebo ($p = 0.0002$ and $p = 0.0113$ for dextromethorphan/quinidine 30/10 and 20/10, respectively).
- The percentage of patients that achieved complete pseudobulbar affect remission (defined as absence of pseudobulbar affect episodes during the patient's final 14 days in the study) was 51.4% in the dextromethorphan 20/quinidine 10 group vs. 29.4% for placebo ($p < 0.05$ and $p < 0.005$ for dextromethorphan/quinidine 30/10 and 20/10, respectively).
- Additionally, the proportion of patients' episode-free days was significantly ($p < 0.005$) greater among dextromethorphan/quinidine 20 mg/10 mg twice daily than placebo recipients at all-time points assessed.
- In all, 283 patients (86.8% of 326) completed the double-blind trial (STAR), including 101 (91.8% of 110) in the dextromethorphan/quinidine 30/10 group, 88 (82.2% of 107) in the dextromethorphan/quinidine 20/10 group, and 94 (86.2% of 109) in the placebo group.
- Without an active comparator trial it remains unclear whether DHQ is superior to other agents. The economic impact of this is significant. It remains unknown if patients who failed to respond to alternate agents would respond to DHQ. The place in therapy of DHQ is not totally elucidated but it may be appropriate to consider it a second line agent except in cases where contraindications to SSRI or TCA exist for specific patients. ALS practice guidelines recommend the use of dextromethorphan/quinidine (Nuedexta) to treat symptoms of PBA, however there is no guidance for use in MS-associated PBA.

Introduction

Dextromethorphan Hydrobromide (20 mg) and Quinidine Sulfate (10 mg) [DHQ] is an oral agent approved by the FDA indicated for the treatment of pseudobulbar affect.

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to considering DHQ for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology[1,2,3]

Pseudobulbar affect (PBA) is a neurologic condition thought to arise in the brainstem where a disconnection in cortical inhibition develops. Dysfunction of serotonin, dopamine, glutamate and sigma-1 receptor systems have been associated with the syndrome. It is hypothesized that excessive glutamatergic activity can manifest in episodes of pseudobulbar affect. Glutamate activity can be regulated through sigma-1 and N-methyl-D-aspartate (NMDA) receptors, and drugs acting on these receptors may be effective in improving the regulation of affect and reducing pseudobulbar affect episodes.

Dextromethorphan is a sigma-1 receptor agonist and uncompetitive NMDA receptor antagonist. Quinidine increases the bioavailability of dextromethorphan by inhibiting cytochrome P450 enzyme 2D6-dependent oxidative metabolism.

Pharmacokinetics/Pharmacodynamics [1,2]

In healthy, normal volunteers DHQ demonstrates a half-life of13 hr. (dextromethorphan); 7 hr. (quinidine) with the peak plasma concentrations occurring at 3-4 hr. (dextromethorphan) and 1-2 hr. (quinidine), respectively.

Metabolism of dextromethorphan occurs in the CYP2D6 system with quinidine's primary pharmacological action competitively inhibiting the metabolism of dextromethorphan catalyzed by CYP2D6 in order to increase and prolong plasma concentrations of dextromethorphan. Quinidine is primarily metabolized by CYP3A4. Approximately 20% of a quinidine dose can be recovered unchanged in the urine. Food does not affect the absorption of DHQ so the daily dose may be given with or without meals.

The effect of dextromethorphan 30 mg/quinidine 10 mg (for 7 doses) on QTc prolongation was evaluate in a randomized, double-blind (except for moxifloxacin), placebo- and positive-controlled (400 mg moxifloxacin) crossover thorough QT study in 50 fasted normal healthy men and women with CYP2D6 extensive metabolizer (EM) genotype. Mean changes in QTcF were 6.8 ms for dextromethorphan 30 mg/quinidine 10 mg and 9.1 ms for the reference positive control (moxifloxacin). The maximum mean (95% upper confidence bound) difference from placebo after baseline correction was 10.2 (12.6) ms. This test dose is adequate to represent the steady state exposure in patients with CYP2D6 extensive metabolizer phenotype.

FDA Approved Indication(s) and Off-label Uses[1]

The DHQ is a combination product containing dextromethorphan hydrobromide (an uncompetitive NMDA receptor antagonist and sigma-1 12 agonist) and quinidine sulfate (a CYP450 2D6 inhibitor) indicated for the treatment of pseudobulbar affect (PBA).

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

As DHQ has not been investigated in patients with pseudobulbar affect with underlying disorders other than ALS or multiple sclerosis, the efficacy of DHQ in other neurological conditions is unknown.

Current VA National Formulary Alternatives[4]

While many agents have been investigate for off label use in PBA, the agents with the best evidence include fluoxetine, citalopram, sertraline, amitriptyline and nortriptyline.

Dosage and Administration[1]

The recommended starting dose of DHQ is 1 capsule daily for the initial 7 days. On the eighth day of therapy and thereafter, the daily dose should be a total of 2 capsules a day, given as 1 capsule every 12 hours.

Hepatic Impairment:

Mild or moderate impairment:. In a study of a combination dose of dextromethorphan 30 mg/quinidine 30 mg twice daily in 12 subjects with mild or moderate hepatic impairment (as indicated by the Child-Pugh method; 6 each) compared to 9 healthy subjects (matched in gender, age, and weight range to impaired subjects), subjects with moderate hepatic impairment showed similar dextromethorphan AUC and Cmax and clearance compared to healthy subjects. Mild to moderate hepatic impairment had little effect on quinidine pharmacokinetics. Patients with moderate impairment showed an increased frequency of adverse events. Therefore, dosage adjustment is not required in patients with mild and moderate hepatic impairment.

Severe impairment: Safety and efficacy not established, although additional monitoring for adverse reactions should be considered. Quinidine clearance is unaffected by hepatic cirrhosis, although there is an increased volume of distribution that leads to an increase in the elimination half-life. Neither dextromethorphan alone nor DHQ has been evaluated in patients with severe hepatic impairment.

Renal Impairment:
Mild or moderate impairment: Dose adjustment not necessary. In a study of a combination dose of dextromethorphan 30 mg/quinidine 30 mg twice daily in 12 subjects with mild (CLCR 50-80 mL/min) or moderate (CLCR 30-50 mL/min) renal impairment (6 each) compared to 9 healthy subjects (matched in gender, age, and weight range to impaired subjects), subjects showed little difference in quinidine or dextromethorphan pharmacokinetics compared to healthy subjects

Severe impairment: Safety and efficacy have not been established as these patients were not included in the clinical trials.

Efficacy

Pseudobulbar Effect Efficacy Measures

Efficacy measures for pseudobulbar affect treatment primarily consist of assessments of episode reduction and episode intensity reduction. The Pathological Laughter and Crying Scale (PLACS)[5] has been used as a measure of the intensity of the pseudobulbar affect episodes. While these scales have proven useful in clinical trials, they are infrequently used in clinical practice. The PLACS is a quantitative, interviewer-rated scale that consists of 18 questions. The Center for Neurologic Study-Lability Scale (CNS-LS) is a short, self-administered questionnaire that is used to screen for symptoms of liability[6], and has been validated in patients with MS and ALS. It is a short (7 item), self-administered questionnaire that provides a quantitative measure of the perceived frequency of pseudobulbar affect episodes

Clinical Trials (refer to Appendix A)

Three large, parallel-group, double-blind, multicenter, industry-sponsored trials have demonstrated efficacy of DHQ in patients with PBA. These studies employed a different dose than the FDA approved product and will not be reviewed in detail here. An initial trial utilized a combination of

dextromethorphan 30 mg plus quinidine 30 mg (DHQ 30/30, n = 65) compared with each drug taken individually at the same dose (dextromethorphan 30, n = 30, or quinidine 30, n = 34) for 28 days.[7] Enrolled patients had ALS and PBA, as indicated by history and a score ≥13 on the CNS-LS. Improvement in CNS-LS score (average of day 15 and 29) was significantly greater in the DHQ 30/30 group than in either the arm with the agents given individually. A second double-blind trial of DHQ 30/30 enrolled patients with MS and clinically diagnosed PBA with baseline CNS-LS scores ≥13.[8] Adjusted mean scores on CNS-LS (averaged across weeks 2, 4, 8 and 12) were significantly reduced in the DHQ 30/30 group versus placebo. The mean number of episodes of laughing and crying per week (from diaries) was also significantly lower for DHQ 30/30 than for placebo.

The STAR[9] trial evaluated two different doses of dextromethorphan/quinidine (DHQ 30/10 and DHQ 20/10) against placebo. Patients with MS or ALS and clinically significant PBA, as defined by a CNS-LS score ≥13, received were randomized for the trial. Episodes of laughing and crying were reported on patient diaries throughout the study, and CNS-LS scores were obtained on weeks 2, 4, 8 and 12. The reduction in daily episode rate was significantly greater in both DHQ groups than for placebo over the twelve week period ($p<0.0001$). Patients in the DHQ 20/10 group reported a mean weekly episode reduction of 82% from baseline vs. a reduction of 47% in the placebo group ($p = 0.001$).Additionally, CNS-LS scores decreased by 8.2 points for both DHQ dosage groups vs. 5.7 points for placebo ($p = 0.0002$ and $p = 0.0113$ for DHQ 30/10 and 20/10, respectively). The percentage of patients that achieved complete PBA remission (defined as absence of pseudobulbar affect episodes during the patient's final 14 days in the study) was 51.4% in the DHQ 20/10 group vs. 29.4% for placebo ($p < 0.05$ and $p < 0.005$ for DHQ 30/10 and 20/10, respectively). Moreover, in both DHQ groups the proportion of patients reporting remission (no episodes throughout the study's final 14 days) was significantly greater than for placebo. Mean reduction in CNS-LS score was also significantly greater than for placebo. Mental Summary mean score on the Medical Outcomes Study 36-Item Short-Form Health Survey (and its subdomains for social functioning and mental health) were significantly improved in the DHQ 30/10 group versus placebo. In all, 283 patients (86.8% of 326) completed the trial. Eighteen patients discontinued due to adverse events (AEs): 10 patients in the DHQ 20/10 group, 6 patients in the DHQ 30/10 group, and 2 patients in the placebo group.

In an open label extension of the STAR trial patients were followed for an additional 12 weeks and those receiving DHQ 30/10.[10] The CNS-LS scores decreased further from those recorded at the start of the open label period, with statistical significance regardless of treatment received during the double-blind phase; however, this reduction was numerically greatest in the group that had previously received placebo.

Adverse Events (Safety Data)[1,2]

Deaths and Other Serious Adverse Events (Sentinel Events)

All reported deaths in the clinical trials occurred in patients with ALS; three recipients of DHQ twice daily and one recipient of placebo died. All were deemed to be the result of progression of the underlying disease.

Frequent adverse reactions:

For DHQ 20/10 adverse events reported by at least 5% of patients were dizziness and diarrhea, headache, nausea, somnolence, fatigue, nasopharyngitis, constipation and dysphagia. Although high-dose quinidine carries cardiac proarrhythmic risk, recipients of the quinidine l0 mg dose in DHQ did not exhibit increased reports of arrhythmias over those patients treated with placebo.

Discontinuation:

A total of 9.3% of DHQ and 1.8% of placebo recipients discontinued study treatment as a result of adverse events.[10] The most common adverse events (incidence of ‡2% and numerically greater than placebo) leading to dextromethorphan/ quinidine 20 mg/10 mg twice-daily discontinuation were muscle spasticity (3%), abdominal pain (2%), asthenia (2%), dizziness (2%) and muscle spasms (2%).

Contraindications

- Hypersensitivity
- History of quinine, mefloquine, or quinidine-induced thrombocytopenia, hepatitis, bone marrow depression, or lupus-like syndrome
- Do not use with other drugs containing quinidine, quinine, or mefloquine
- Coadministration of MAOIs or use within 14 days
- Do not use with drug that both prolong QT interval and are metabolized by CYP2D6 (eg, thioridazine, pimozide)
- Complete AV block (without implanted pacemakers)
- Prolonged QT interval, congenital long QT syndrome, or history of torsades de pointes
- Heart failure

Look-alike / Sound-alike (LA / SA) Error Risk Potential

As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Dextromethorphan/quinidine 20/10mg	None	None	None	Dextromethorphan/chlorpheniramine Dextromethorphan/guaifenesin Dextromethorphan/phenylephrine Dextromethorphan/promethazine Dextromethorphan/pseudoephedrine
Nuedexta	Neulasta	None	Neulasta	Neumega Nesina Nucynta

Drug Interactions [1,2]

The potential for DHQ to inhibit or induce cytochrome P450 *in vitro* were evaluated in human microsomes. Dextromethorphan did not inhibit (< 20% inhibition) any of the tested isoenzymes: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 in human liver microsomes at concentrations up to 5 microM. Quinidine did not inhibit (< 30% inhibition) CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A4 in human microsomes at concentrations up to 5 microM. Quinidine inhibited CYP2D6 with a half maximal inhibitory concentration (IC_{50}) of less than 0.05 microM. Neither dextromethorphan nor quinidine induced CYP1A2, CYP2B6 or CYP3A4 in human hepatocytes at concentrations up to 4.8 microM.

Therapy with medications that are primarily metabolized by CYP2D6 and that have a relatively narrow therapeutic index should be initiated at a low dose if a patient is receiving DHQ concurrently. If DHQ is added to the treatment regimen of a patient already receiving a drug primarily metabolized by CYP2D6, the need for a dose modification of the original medication should be considered (e.g. dosage above 35 mg/day for paroxetine is not recommended). The extent to which CYP2D6 interactions may pose clinical problems will depend on the pharmacokinetics of the substrate involved. When used with selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine or tricyclic antidepressants (TCAs) such as clomipramine and imipramine), DHQ may cause “serotonin syndrome”, with changes including altered mental status, hypertension, restlessness, myoclonus, hyperthermia, hyperreflexia, diaphoresis, shivering, and tremor. Potentially harmful drug-drug interactions have also been suggested for DHQ when coadministered with drugs that prolong the QT interval.

Pharmacoeconomic Analysis

There are no published pharmacoeconomic models for DHQ.

Conclusions

The current medical literature suggests that PBA is a treatable condition. However, the majority of evidence assessing pharmacotherapy for the condition has been evaluated by open label studies, case series and small sample size trials. Additionally, many studies did not use the same scales to measure improvement in PBA episodes so comparison between agents is difficult. There have been no head to head comparisons of DHQ and traditional agents such as citalopram, paroxetine, amitriptyline or sertraline. The initial trials of DHQ evaluated different strengths of dextromethorphan and quinidine so extrapolation of those doses than the FDA approved dose of dextromethorphan 20 mg and quinidine 10 mg is difficult. The STAR trial evaluated DHQ versus placebo and provides the most robust data to date. It is the largest, longest, blinded and randomized trial to date. The trial used quantitative scales which have been validated in PBA to assess efficacy. The results of the trial demonstrated clear superiority of DHQ over placebo in the efficacy measures of CNS-LS and daily PBA episodes. Without an active comparator trial it remains unclear whether DHQ is superior to other agents. The economic impact of this is significant. It remains unknown if patients who failed to respond to alternate agents would respond to DHQ. The place in therapy of DHQ is not totally elucidated but it may be appropriate to consider it a second line agent except in cases where contraindications to SSRI or TCA exist for specific patients.

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